Madrigal Pharmaceuticals to Present Secondary Analyses of Data from Phase 2 NASH Study of Resmetirom and Symposium at the Digital International Liver Congress™ 2020

August 26, 2020

CONSHOHOCKEN, Pa., Aug. 26, 2020 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL) announced today that on Friday, August 28, 2020 at the Digital International Liver Congress ™2020, European Association for the Study of the Liver (EASL), secondary analyses of data from its Phase 2 NASH study with MGL-3196 (resmetirom) will be presented. Resmetirom is currently in Phase 3 development for the treatment of NASH patients with stage 2-3 fibrosis (ClinicalTrials.gov NCT03900429 and ClinicalTrials.gov/NCT04197479).

Rohit Loomba, MD, MHSc, Professor of Medicine (with tenure), Division of Gastroenterology, Department of Medicine, and Director, NAFLD Research Center and Director, Liver Epidemiology Training Program, University of California at San Diego, will present “Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) to predict treatment response on NASH liver biopsy: a secondary analysis of the resmetirom randomised placebo-controlled phase 2 clinical trial” (AS077), during the Abstract session: NAFLD - Pharmacological Therapy, on Friday, August 28, 2020, at 12:00 PM CET (6:00 AM EDT). Registered attendees will be able to watch the live presentation on the Digital ILC 2020 website, Channel 3.

Dr. Loomba commented, “MRI-PDFF reduction has been shown to be associated with improvement in NASH components as assessed on liver biopsy. These secondary analyses of Madrigal’s Phase 2 NASH clinical trial add significant additional insight into the potential of PDFF to predict NASH response. These findings support the pathogenicity of liver steatosis in NASH and fibrosis progression.“

Madrigal is excited to host four presentations by NASH experts, Impacting NASH: Focus on Liver and Cardiovascular Benefits, that registered attendees will be able to access via the Madrigal virtual booth on the Digital ILC 2020 website, on Friday, August 28, 2020, beginning at 1:00 PM CET. The presentations will also be available via the Newsroom-Webcasts page on Madrigal’s website beginning at the same time:

- “Epidemiology of NASH: CV- and Liver-related Outcomes”
  Zobair Younossi, MD, MPH, FACP, FACG, AGAF
  Chairman, Department of Medicine, Inova Fairfax Medical Campus. He is also Professor of Medicine, Virginia Commonwealth University, Inova Campus and Affiliate Professor of Biomedical Sciences at George Mason University.
  - Dr. Younossi focuses on global prevalence and trends in NAFLD/NASH, including the comprehensive burden of clinical, economic, and quality of life factors associated with the disease.

- “Resmetirom for the Treatment of NASH”
  Stephen A. Harrison, MD
  Visiting Professor of Hepatology, Radcliffe Department of Medicine, University of Oxford, Oxford, England and Medical Director Pinnacle Clinical Research San Antonio, TX
    - Dr. Harrison discusses the non-invasive and clinical identification of patients at high risk for NASH with fibrosis, highlighting findings from the resmetirom clinical trial program.

- “Real-life Treatment of NASH: Non-invasive Imaging in NASH Diagnosis and Treatment. Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) to Predict Benefit in Patients with NASH: Focus on Resmetirom”
  Rohit Loomba, MD, MHSc
  Professor of Medicine (with tenure), Division of Gastroenterology, Department of Medicine, and Director, NAFLD Research Center and Director, Liver Epidemiology Training Program, University of California at San Diego
    - Dr. Loomba provides an overview of MRI-PDFF as a non-invasive diagnostic for NASH and discusses findings from a secondary analysis of the resmetirom Phase 2 study that examine MRI-PDFF response as a predictor of histologic response in patients with NASH.

- “The Intersection of CVD and NASH, the Next CVD Prevention Frontier”
  Seth Baum, MD, FACC, FACPM, FAHA, FNLA,FASPC
  Founder and CEO, Excel Medical Clinical Trials, and Clinical Affiliate Professor of Medicine at Florida Atlantic University (FAU) Medical School in Boca Raton, FL
    - Dr. Baum highlights topics of dyslipidemia, carotid-artery intimal medial thickness (CIMT), coronary artery calcification (CAC), and cardiovascular mortality in NAFLD/NASH, in addition to the role of resmetirom as experts consider cardiovascular disease in the NASH treatment landscape.

About Resmetirom (MGL-3196)
Thyroid hormone, through activation of its β-receptor in hepatocytes, plays a central role in liver function impacting a range of health parameters from levels of serum cholesterol and triglycerides to the pathological buildup of fat in the liver. Thyroid hormone receptor (THR)-β action in the liver is key to proper function of the liver, including regulation of mitochondrial activity such as breakdown of liver fat and control of the level of normal, healthy mitochondria. Patients with NASH have reduced levels of thyroid hormone activity in the liver with resultant impaired hepatic function, in part due to the inflamed state of the liver that causes degradation of thyroid hormone.

To exploit the thyroid hormone receptor (THR)-β pathway for therapeutic purposes in cardio-metabolic and liver diseases, it is important to avoid activity at the THR-α receptor, the predominant systemic receptor for thyroid hormone that is responsible for activity outside the liver including in heart and bone. The lack of selectivity of older thyromimetic compounds, chemically-related toxicities and undesirable distribution in the body led to safety concerns. Madrigal recognized that greater selectivity for thyroid hormone receptor (THR)-β and liver targeting might overcome these challenges and deliver the full therapeutic potential of THR-β agonism. Resmetirom has been shown to be highly selective based on 1) THR- β receptor functional selectivity based on both in vitro and in vivo assays 2) specific uptake into the liver, its site of action, virtually avoiding any uptake into tissues outside the liver. In short and long term human and animal studies, resmetirom has been confirmed to be safe and devoid of activity at the THR-α receptor and without impact on

bone or cardiac parameters. Resmetirom does not impact the thyroid axis hormones, including the central thyroid axis. Madrigal believes that resmetirom is the first orally administered, small-molecule, liver-directed, truly β-selective THR agonist.

About the Phase 3 Registration Program for the Treatment of NASH (Non-alcoholic steatohepatitis)
Analyses from the resmetirom Phase 2 NASH study demonstrate that the magnitude of liver fat reduction accurately predicts NASH resolution and liver fibrosis reduction and, specifically, that the resmetirom doses being used in Madrigal's Phase 3 MAESTRO- NASH trial could achieve the level of fat reduction predictive of NASH resolution and fibrosis reduction [Madrigal COVID and ABSTRACT Press Release_20200414].

The Phase 3 MAESTRO-NASH trial is expected to enroll 900 patients with biopsy-proven NASH (fibrosis stage 2 or 3), randomized 1:1:1 to receive resmetirom 80 mg once a day, 100 mg once a day, or placebo. After 52 weeks of treatment a second biopsy is performed. The primary surrogate endpoint on biopsy will be NASH resolution, with at least a 2-point reduction in NAS (NASH Activity Score), and with no worsening of fibrosis. Two key secondary endpoints are liver fibrosis improvement of at least one stage, with no worsening of NASH, and lowering of LDL-cholesterol [ClinicalTrials.gov/NCT03900429].

A second 52-week Phase 3 multi-center, double-blind, randomized, placebo-controlled study of resmetirom, MAESTRO-NAFLD-1, was initiated in December 2019 in 700 patients with non-alcoholic fatty liver disease (NAFLD), presumed NASH, randomized 1:1:1 to receive resmetirom 80 mg once a day, 100 mg once a day, or placebo. MAESTRO-NAFLD-1 also includes a 100 mg resmetirom open label arm in up to 100 patients. Unlike MAESTRO-NASH, MAESTRO-NAFLD-1 is a non-biopsy study and represents a "real-life" NASH study. NASH or presumed NASH is documented using historical liver biopsy or non-invasive techniques including fibroscan and MRI-PDFF. Using non-invasive measures, MAESTRO-NAFLD-1 is designed to provide incremental safety information to support the NASH indication as well as provide additional data regarding clinically relevant key secondary efficacy endpoints to better characterize the potential clinical benefits of resmetirom on cardiovascular and liver related endpoints. These key secondary endpoints include LDL-cholesterol, apolipoprotein B and triglyceride (TG) lowering; reduction of liver fat as determined by magnetic resonance imaging, proton density fat fraction (MRI-PDFF); and reduction of PRO-C3, a NASH fibrosis biomarker. [ClinicalTrials.gov/NCT04197479] Additional secondary and exploratory endpoints will be assessed including reduction in liver enzymes, fibroscan scores and other fibrosis and inflammatory biomarkers.

These and other data, including safety parameters, form the basis for potential subpart H submission to FDA for accelerated approval for the treatment of NASH. The original 900 patients in the MAESTRO-NASH study will continue on therapy after the initial 52-week treatment period; up to another 1,100 patients are to be added using the same randomization plan and the study is expected to continue for up to 54 months to accrue and measure clinical events, most relevantly progression to cirrhosis.

About Resmetirom's Potential to Confer Cardiovascular Risk Reduction in NASH patients
Additionally, resmetirom lowers multiple atherogenic lipids, including LDL cholesterol, apolipoprotein B, triglycerides, and lipoprotein (a), as demonstrated in Phase 2, a key differentiating factor compared with other NASH therapeutics. The magnitude of reduction of these lipids support a potential indication for treatment of hyperlipidemia in NASH patients and predicts a potential for

benefit on cardiovascular (CV) events in NASH patients who die most frequently of CV, not liver disease.

Because of their diabetes, dyslipidemia, hypertension, obesity in concert with an inflamed, fatty liver, NASH patients, particularly those with advanced fibrosis, are at a substantially increased CV risk compared to the general population. Resmetirom's ability to decrease liver fat, which is an independent risk factor for CV events, and resmetirom's effect to reduce atherogenic lipids are being further evaluated in several key secondary endpoints in both MAESTRO Phase 3 clinical studies.

About Madrigal Pharmaceuticals

Madrigal Pharmaceuticals, Inc. (Nasdaq: MDGL) is a clinical-stage biopharmaceutical company pursuing novel therapeutics that target a specific thyroid hormone receptor pathway in the liver, which is a key regulatory mechanism common to a spectrum of cardio-metabolic and fatty liver diseases with high unmet medical need. Madrigal's lead candidate, resmetirom, is a first-in- class, orally administered, small-molecule, liver-directed, thyroid hormone receptor (THR)-β selective agonist that is in currently in two Phase 3 clinical studies, MAESTRO-NASH and MAESTRO-NAGLD-1, designed to demonstrate multiple benefits across a broad spectrum of NASH (non-alcoholic steatohepatitis) and NAFLD (non-alcoholic fatty liver disease) patients. For more information, visit www.madrigalpharma.com.

Forward-Looking Statements

This communication contains "forward-looking statements" made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, that are based on our beliefs and assumptions and on information currently available to us, but are subject to factors beyond our control. Forward-looking statements include but are not limited to statements or references concerning: our clinical trials; research and development activities; the timing and results associated with the future development of our lead product candidate, MGL-3196 (resmetirom); our primary and secondary study endpoints for resmetirom and the potential for achieving such endpoints and projections; optimal dosing levels for resmetirom; projections regarding potential future NASH resolution, safety, fibrosis treatment, cardiovascular effects, lipid treatment or biomarker effects with resmetirom; the predictive power of liver fat reduction on NASH resolution with fibrosis reduction or improvement; *the achievement of enrollment objectives concerning patient number, safety database and/or timing for our studies; potential NASH or NAFLD patient risk profile benefits with resmetirom; and our possible or assumed future results of operations and expenses, business strategies and plans, capital needs and financing plans, trends, market sizing, competitive position, industry environment and potential growth opportunities, among other things. Forward-looking statements: reflect management's current knowledge, assumptions, judgment and expectations regarding future performance or events; include all statements that are not historical facts; and can be identified by terms such as "anticipates," "be," "believes," "continue," "could," "demonstrates," "design," "estimates," "expects," "forecasts," "future," "goal," "hopeful," "intends," "may," "might," "plans," "potential," "predicts," "predictive," "projects," "seeks," "should," "will," "would" or similar expressions and the negatives of those terms. Although management presently believes that the expectations reflected in such forward-looking statements are reasonable, it can give no assurance that such expectations will prove to be correct and you should be aware that actual results could differ materially from those contained in the forward-looking statements.*

Forward-looking statements are subject to a number of risks and uncertainties including, but not limited to: our clinical development of resmetirom; enrollment uncertainties, generally and in relation

to COVID-19 shelter-in-place and social distancing measures and individual precautionary measures that may be implemented or continued for an uncertain period of time; outcomes or trends from competitive studies; the risks of achieving potential benefits in studies that includes substantially more patients than our prior studies; the timing and outcomes of clinical studies of resmetirom; and the uncertainties inherent in clinical testing. Undue reliance should not be placed on forward-looking statements, which speak only as of the date they are made. Madrigal undertakes no obligation to update any forward-looking statements to reflect new information, events or circumstances after the date they are made, or to reflect the occurrence of unanticipated events. Please refer to Madrigal's filings with the U.S. Securities and Exchange Commission for more detailed information regarding these risks and uncertainties and other factors that may cause actual results to differ materially from those expressed or implied. We specifically discuss these risks and uncertainties in greater detail in the section entitled "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2019 and our Quarterly Report on Form 10-Q for the period ended June 30, 2020, as well as in our other filings with the SEC.

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